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| EXAMINER | |
|---|---|
| PANDE, SUCHIRA | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/549,389 | KANAOKA, SHIGERU | |
| | Examiner | Art Unit | |
| | SUCHIRA PANDE | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 January 2008 and 04 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6 and 13-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 28, 2008 and February 4, 2008 have been entered.

## *Claim Status*

2. In the amendment filed on February 4, 2008 applicant has cancelled claims 7-12. Amended claims 1, 3, 5, 17-20 and added new claims 21-23. Currently claims 1-6, 13-23 are pending in this application and will be examined in this action.

### *Information Disclosure Statement*

3. The information disclosure statement (IDS) submitted on January 28, 2008 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Response to Arguments*

Re rejection of claims 1-5, 13-14, 17-19 under 102 over Alexander and Raicht

4. Applicant's arguments filed January 28, 2008 have been fully considered but they are not persuasive. Applicant has amended base claim, the subject matter of instant amended claim is still anticipated by teaching of Alexander and Raicht.

The newly added claims 21-23 refer to human feces. Since cited art taught stool from humans as starting material, the newly added claims are also anticipated by previously cited art.

Therefore the previously cited 102 rejection over Alexander and Raicht are being maintained.

Re unexpected results

5. Cited prior art anticipates the claimed invention and 102 (b) rejection is pending, hence arguments re unexpected results cited are moot. Unexpected results can only help overcome a 103 obviousness type rejection not a 102 (b) rejection.

Applicant refers to Example 2 on pages 10-11 of the specification and states this provides support of unexpected results of applicant's present claims over the Alexander and Raicht reference cited by Examiner.

Examiner would like to point out, in the situation when only 103 rejections are pending, unexpected results can be considered by Examiner. In that situation, Applicant would need to provide comparative data obtained using the claimed method and method taught by cited art where applicant clearly points out what the unexpected results are. This should be accompanied by discussion that indicates to one of ordinary skill why these results are unexpected and what aspect of the claimed invention makes this claimed invention unexpectedly better than the method taught by cited art.

Re rejection of claims 6, 20, 15 and 16 under 103 over Alexander and Raicht further in view of appropriate secondary references

6. Since 102 rejections are being maintained. The 103 rejections of claims 6, 20, 15 and 16 under 103 over Alexander and Raicht further in view of appropriate secondary references are also being maintained.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-5, 13-14, 17-19, 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexander and Raicht (1998) Digestive Diseases and Sciences Vol. 43 No. 12 pp 2652-2658 as evidenced by Ultraspec™-II RNA isolation system Biotecx Bulletin No. 28, 1993.

Regarding claim 1, Alexander and Raicht teaches a method for preparing a sample to extract RNA (see title where Total RNA purification from Human stool sample is taught) used in a tumor marker detecting method (see abstract where RNA isolated from human stool shown to be useful for detecting human mRNA is taught) for diagnosing colon cancer (See page 2652 par.1-2, where colon neoplasia and methods of diagnosing it are taught) consisting of:

a) homogenizing a collected biological (human stool) sample in the presence of an RNase inhibitor (Ultraspec II reagent from Biotecx Laboratories contains chaotropic

agent 14 M guanidium salt that are potent inhibitors of Rnase), to prepare a suspension thereof (See page 2653 Materials and Methods par. 2-4 under Purification of total RNA from stool samples); without separating cell components from the biological sample (the method taught by Alexander and Raicht directly homogenizes the stool without separating cell components see page 2653 where frozen piece of stool is made into a slurry (in a solution containing EDTA which is a well known chelating agent routinely used by one of ordinary skill in the art to inhibit RNAse activity) and particulates are removed from the suspension by decantation followed by lysis using the Ultraspec II reagent from Biotecx Laboratories) and

b) extracting the RNA to provide extracted RNA (see page 2653 section purification of RNA )

Thus, claim 1 is anticipated by Alexander and Raicht.

Regarding claims 2 and 17, Alexander and Raicht teach wherein the collected biological sample is frozen (see page 2653 par. 2 under Purification of Total RNA from Stool Samples, where freezing for Stool sample in Liquid Nitrogen is taught).

Regarding claims 3 and 18, Alexander and Raicht teaches wherein the Rnase inhibitor is guanidine thiocyanate (Alexander and Raicht teach use of Ultraspec II reagent, a single step RNA purification from Biotecx Laboratories. This reagent contains 14 M solution of guanidine salts. The formulation is based on a method of Chomczynski and Sacchi that uses guanidinium thiocyanate-phenol-chloroform for RNA isolation. See Biotecx Bulletin No:28, 1993, Introduction and Reference no 3.).

Regarding claims 4 and 19 Alexander and Raicht teach wherein the biological sample is feces (see Title where stool samples ie. feces is taught).

Regarding claim 5, Alexander and Raicht teach a tumor marker detecting method for diagnosing colon cancer comprising:

a) providing extracted RNA by the method of claim 1; (see page 2653 section titled: Purification of total RNA from stool samples) (see page 2653 par. 3-4 where RNA extraction is taught))

b) carrying out reverse transcription on the extracted RNA from step (a) to provide cDNA (see page 2654 par. 3-4 where RT-PCR is taught);

c) amplifying the cDNA from step (b) (see page 2654 par. 5-6 where PCR amplification of cDNA is taught); and

d) detecting the amplified cDNA from step (c) wherein the tumor marker is thereby detected (see page 2654 par. 7 and Results par. 3 where detection of amplified cDNA by gel electrophoresis is taught. Thus teaching detection of selected marker)

Regarding claim 13, Alexander and Raicht teach wherein the biological sample comprises microorganisms (see page 2656 par.1 where presence of intestinal bacteria in the human stool is taught. by this teaching Alexander and Raicht teach wherein the biological sample (stool) comprises microorganisms ).

Regarding claim 14, Alexander and Raicht teach wherein in step b) whole RNA is extracted from the sample obtained from step a) without separating RNA derived from human cells from RNA derived from bacteria (see title of section TOTAL RNA

extraction—this inherently teaches no separation of RNA was done. All the RNA from any kind of human or bacterial cell that was present in the sample was extracted.

Regarding claims 21, 22, Alexander and Raicht teach wherein the feces is human feces (see title where human stool is taught)

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 6 and 20, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander and Raicht (1998) Digestive Diseases and Sciences Vol. 43 No. 12 pp 2652-2658 as evidenced by UltraspecTM-II RNA isolation system Biotecx Bulletin No. 28, 1993 in view of Sano et al. (1995) Cancer Research 55: 3785-3789.

Regarding claim 6, Alexander and Raicht teach method of claim 1 but do not teach wherein the tumor marker is COX-2.

Regarding claim 20, Alexander and Raicht teach wherein the collected biological sample is frozen (see page 2653 par. 2 under Purification of Total RNA from Stool Samples, where freezing for Stool sample in Liquid Nitrogen is taught).

Regarding claim 20, Alexander and Raicht teaches wherein the Rnase inhibitor is guanidine thiocyanate (Alexander and Raicht teach use of Ultraspec II reagent, a single step RNA purification from Biotecx Laboratories. This reagent contains 14 M solution of guanidine salts. The formulation is based on a method of Chomczynski and Sacchi that

uses guanidinium thiocyanate-phenol-chloroform for RNA isolation. See Biotecx Bulletin No:28, 1993, Introduction and Reference no 3.).

Regarding claim 20 Alexander and Raicht teach wherein the biological sample is feces (see Title where stool samples ie. feces is taught).

Regarding claim 23 Alexander and Raicht teach wherein the feces is human feces (see Title where human feces is taught).

Regarding claim 6, Sano et al. teach wherein the tumor marker is COX-2 (see abstract where COX-2, a colon cancer marker is taught)

It would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to use COX-2 tumor marker taught by Sano et al. in the method of Alexander and Raicht for diagnosing colon cancer. The motivation to do so is provided by Sano et al.

Sano et al. show enhanced expression of the COX-2 gene in colon cancer tissues. They state " Moreover, the immunoreactive COX-2 was abundant in colonic cancer cells in our study. COX-2 may assume an important role in the activation pathways by which carcinogens can be converted to the reactive intermediates that mutate DNA. These findings suggest that COX-2 induced by stimulation of chemical substances, cytokines, and growth factors may have a role in the initiation, promotion, and maintenance of colorectal cancers" (see page 3788 last 2 paragraphs)

11. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander and Raicht (1998) Digestive Diseases and Sciences Vol. 43 No. 12 pp 2652-2658 as evidenced by UltraspecTM-II RNA isolation system Biotecx Bulletin No.

28, 1993 in view of Godfrey et al. (US Pat. 7101663 B2 issued September 5, 2006 filed on March 4, 2002).

Regarding claim 15, Alexander and Raicht teach the method of claim 5 and teach RT PCR. But do not teach wherein in step d) amplifying the cDNA from step c) is carried out by a nested PCR.

Regarding claim 15, Godfrey et al. teach wherein in step d) amplifying the cDNA from step c) is carried out by a nested PCR (see col 15 line 61 where nested PCR is taught).

Regarding claim 16, Godfrey et al. teach, wherein the amplification is carried out by a PCR and a first round of the PCR is executed for 20 cycles (see col. 20 lines 19-20 where Godfrey et al. teach PCR is carried out in two 20-cycle steps. Thus Godfrey et al. teach wherein the amplification is carried out by a PCR and a first round of the PCR is executed for 20 cycles).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Godfrey et al. in the method of Alexander and Raicht at the time the invention was made. The motivation to do so is provided to one of ordinary skill in the art by Godfrey et al. who state " Quantitative RT-PCR is a sensitive technique and is particularly useful for the analysis of samples containing limited amounts of nuclei acids, such as in clinical tissues------. When quantitating these small amounts of RNA and/or very low abundance mRNA species, obtaining maximum sensitivity from a quantitative RT-PCR is extremely important. While consecutive rounds of nested PCR are often used to obtain maximum sensitivity, this is difficult to achieve and still maintain accurate

quantitation. Furthermore, multiple rounds of PCR increase the risk of contamination, a serious problem when working at desired sensitivity levels. One tube RT-PCR reduces the risk of contamination ------because the reaction tubes are never opened. Theoretically, a one tube procedure should have the same sensitivity as a two step approach (separate RT followed by PCR) but in practice this is not the case". (see col. 15 lines 28-43). They go on to list out the reasons why this is the case. Finally they state "In a two –step or **nested RT-PCR procedure**, specificity can be achieved with the use if hot-start PCR and a primer set 5' upstream from the RT primer. However, this is not the case in a one –tube procedure unless one is willing to open the reaction tube to add new primers (thus making it a one –tube but two step procedure). It has been hypothesized that by using an external RT primer and keeping the RT and PCR primers separated during the RT step, PCR specificity and therefore sensitivity in a one –tube RT-PCR should be maintainable------Here, a modified one –tube RT-PCR assay that greatly increases sensitivity and can be used for quantitative RT-PCR----is presented." (see col 15 lines 61- col. 16 line 5). Thus explicitly teaching to one of ordinary skill that by using this modified method one can perform ***nested PCR*** in one tube closed format and at the same time have a sensitive quantitative RT-PCR.

***Conclusion***

12. All claims under consideration 1-6, 13-23 are rejected over prior art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa E Strzelecka/

Primary Examiner, Art Unit 1637

May 1, 2008